Health Effects of Dissolvable Tobacco Products

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Overview

- Background
- Pharmacology
- CDER Experience with Nicotine Replacement Therapy (NRT) products

Background

- Information available on health effects of DTPs typically limited to data on systemic nicotine exposure, biomarker analysis, or intermediate clinical outcomes such as heart rate and blood pressure
- Can we learn from experiences of other oral tobacco and nicotine products to help us understand what health effects might be expected from DTPs?

Information from Smokeless Tobacco Experience

- Use of traditional smokeless tobacco (ST) products such as snuff, chewing tobacco or snus, is linked to cancerous and non-cancerous oral cavity effects, cancers of the esophagus and pancreas, heart diseases, and reproductive problems
- The 1986 Surgeon General report was written prior to development of DTPs, however, it gives us some guidance as to where we might focus our clinical research regarding possible health effects from DTPs

Product Attributes are Key

- Ingredients and characteristics of a specific product are key to understanding its potential toxicity
- Tobacco products may be designed to have a number of desired characteristics such as nicotine concentration, pH and amount free nicotine, or nicotine-release and dissolution characteristics
- The attributes of individual products must be kept in mind when considering the safety both between and within a class of products

The Oral Experience

- DTPs have distinct characteristics from traditional ST in that they are typically fully consumed tobacco products with the oral experience lasting less than 15-30 minutes/episode as compared to other smokeless products that are kept in the oral cavity for prolonged periods of time and then removed.

Oral Health Effects

- Investigators have provided differing reports of the extent of detrimental oral health effects from ST. A major factor may be that individual ST differ in their content characteristics due to various manufacturing processes as well as differences in actual use, there could also be confounding factors - other tobacco or alcohol use.

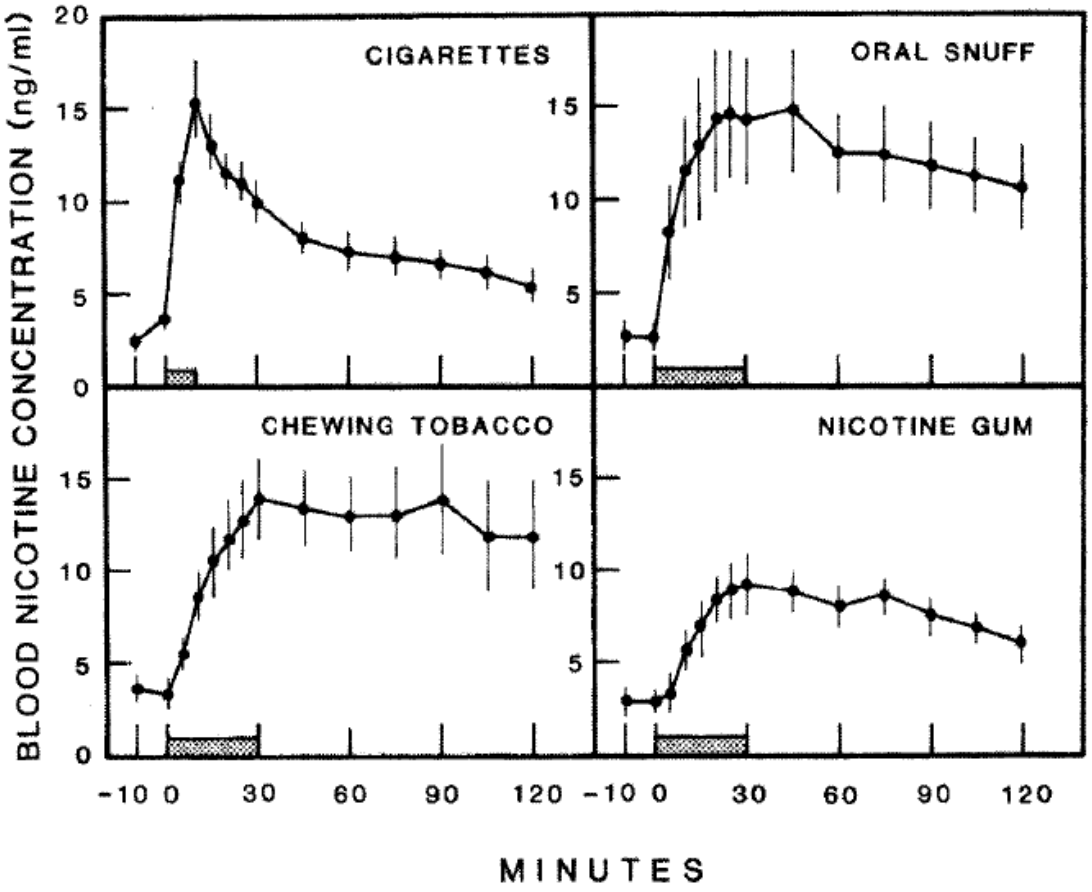
- There is concern that use of DTPs may increase risk for oral diseases. As discussed in the previous slide DTPs can be a subtype of ST, however, there are likely significant differences not only in the manner in which these products are consumed but also differences in product characteristics

Oral Health Effects (2)

- Epidemiological studies from USA, India, Pakistan, and Sweden provide sufficient evidence that ST causes oral cancer in humans. The risk of oral cancer from ST use has been mainly attributed to TSNA content although other constituents likely have contributing roles.
- More commonly, use of American ST are associated with mucosal lesions aside from dysplasia or cancer including, keratosis and periodontal effects such as gingival recession.
- As some products can have a high content of sugar, ST users can be at risk for increased dental cavities. Tooth staining and staining of prosthetic devices such as dentures, can also occur.
- How the experiences of traditional American ST use on oral health applies to use of dissolvable products is unknown.

Photos from: Greer R. Oral manifestations of smokeless tobacco use. *Otolaryngol Clin North Am.* 2011;44(1):31-56.

Nicotine delivery kinetics are different for various tobacco products



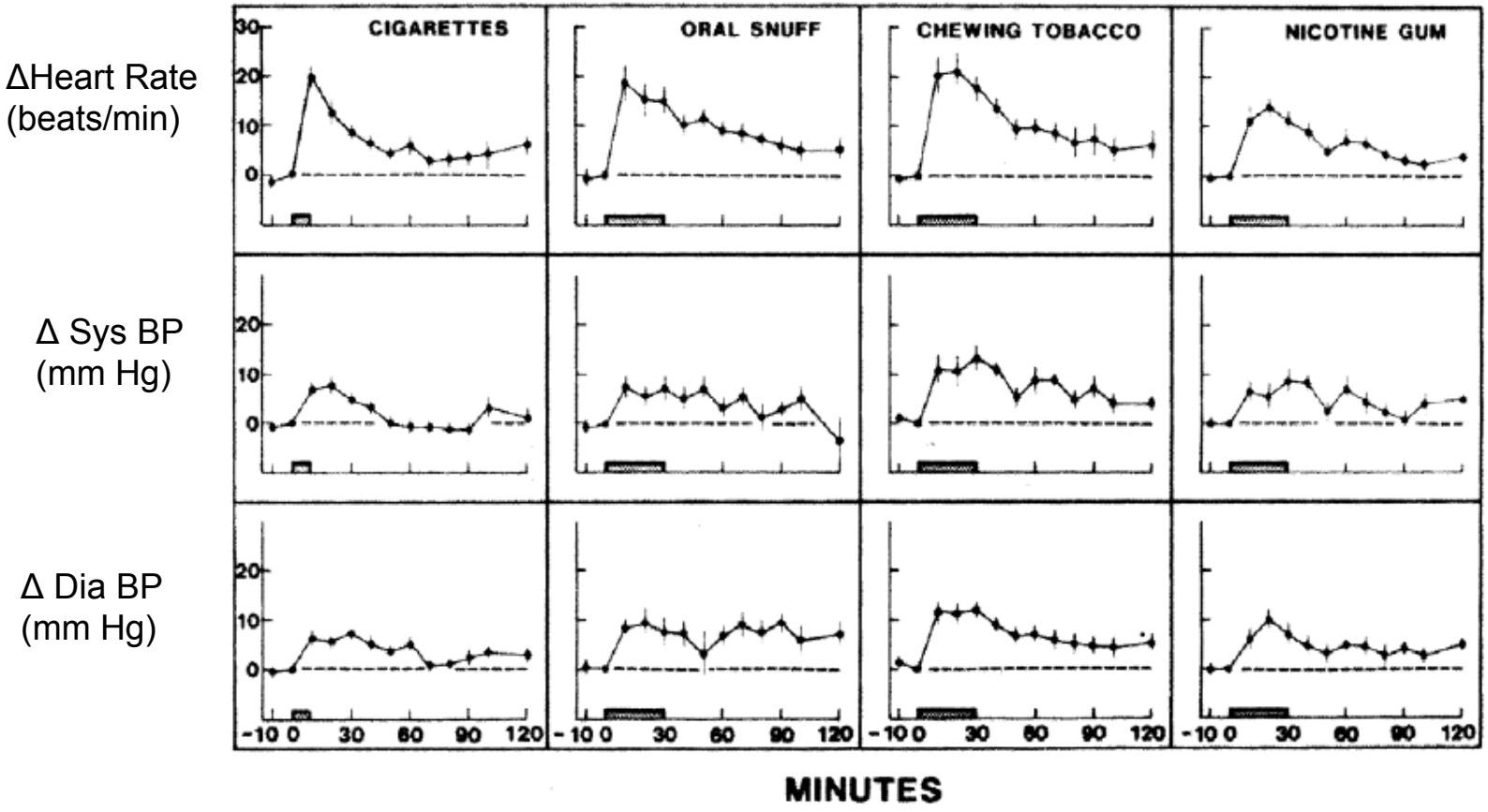
Benowitz N et al. Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*.1988;44(1):23-8.

Study Results

- Smoking was shown to produce rapid peaks and troughs of plasma nicotine, whereas using ST products result in more sustained levels of nicotine up to one hour
- Peak levels seen with smoking and ST are similar, but blood levels of nicotine fall more slowly after ST or nicotine gum due to continuing absorption
- Total absorbed dose from ST is greater than from cigarettes

Cardiovascular Response to Variable Tobacco Products

BP and HR are altered differently by product, but impact on actual health outcome is not known

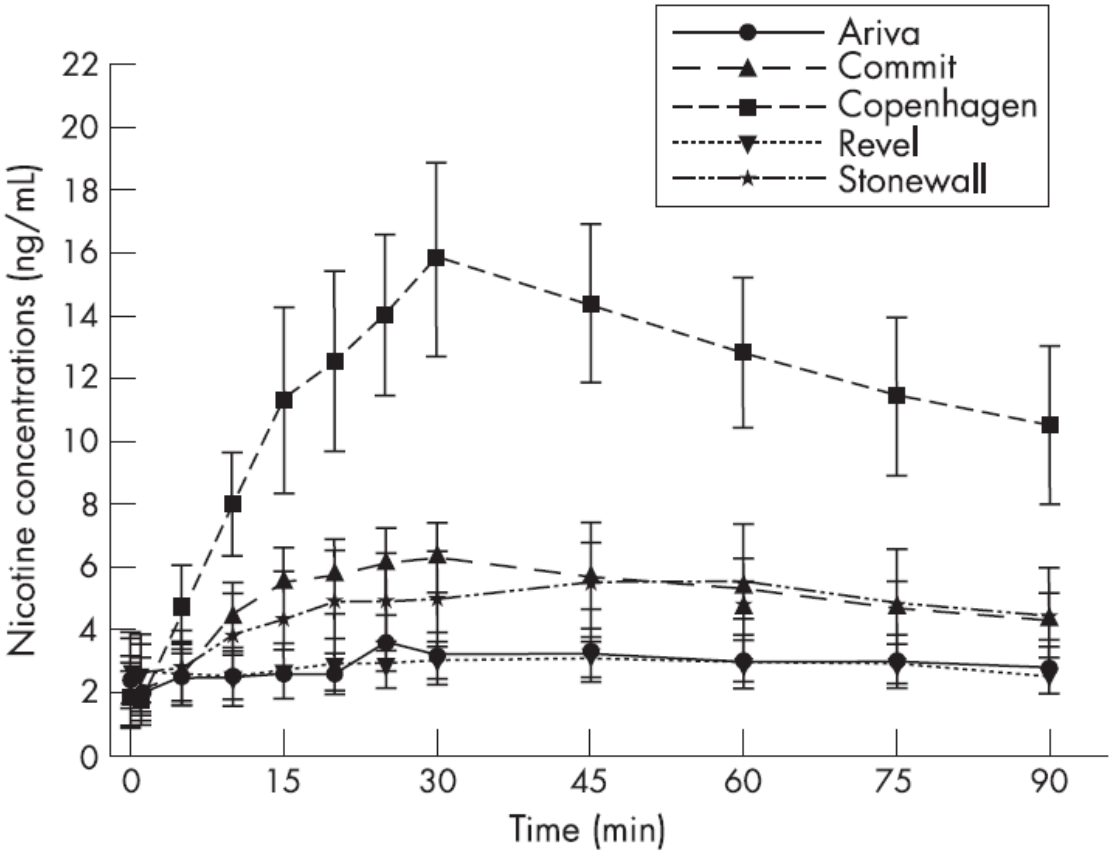


Benowitz N et al. Nicotine absorption and cardiovascular effects with smokeless tobacco use: Comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther.*1988;44(1):23-8.

Examples of Nicotine Loads by Product

- Ariva: 1.5 mg nicotine
- Stonewall: 4 mg nicotine
- Camel: Strip-0.6 mg, Orb-1 mg, Stick-3 mg
- Commit: Lozenge- 2 mg or 4mg

Product characteristics impact the plasma nicotine concentrations of dissolvable and other smokeless tobacco products



Kotlyar M et al. Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tobacco Control.* 2007;16:138-42. [14]

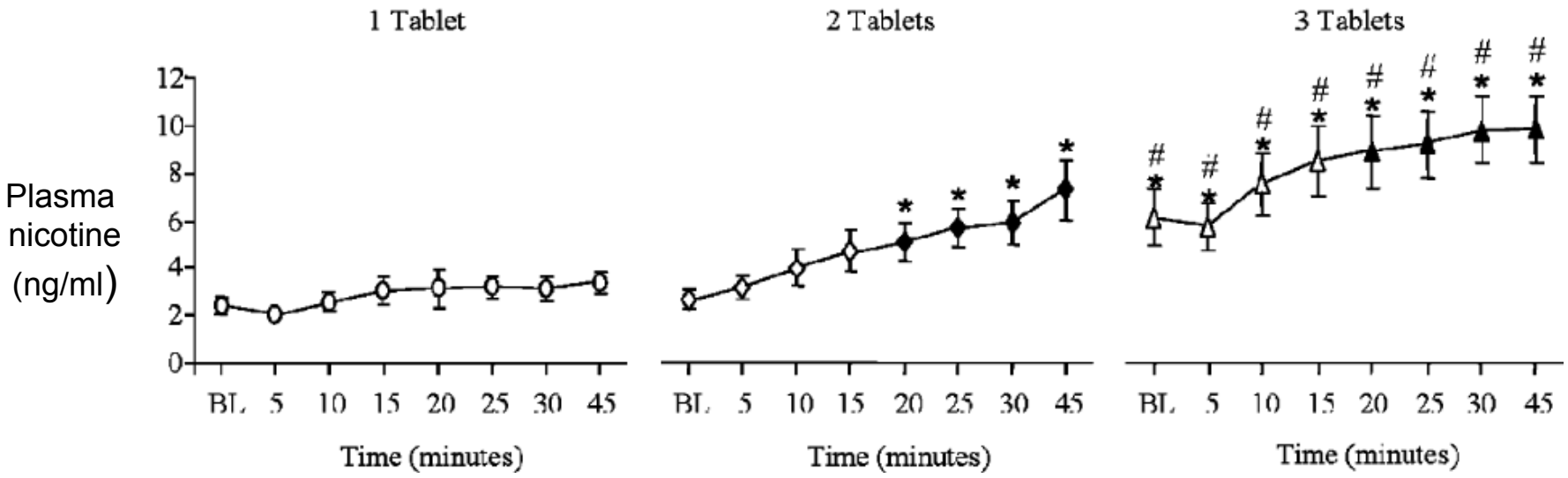
2010 Study by Cobb et al.

- Six products evaluated: Ariva, Camel Snus, Self-selected cigarette, sham cigarette, or Commit (2mg)
- Outcome measures: plasma nicotine, expired carbon monoxide (CO), heart rate, and subjective effects
- Nicotine increases were greatest for self selected cigarette
- For heart rate a significant increase over time were seen for both self-selected cigarettes and Camel snus, however, no significant increases were seen for Ariva, Commit, or Marlboro Snus.
- CO increased for non-sham combustible products but no significant changes noted for non-combustible products.

Cobb C et al. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tob Control*. 2010;19(5):367-73.

Effect of Product Quantity

Plasma nicotine level varies with number of tablets ingested



*=significant difference from 1 tablet at same time
#=significant difference from 2 tablets at same time

Blank M et al. Nicotine delivery, cardiovascular profile, and subjective effects of an oral tobacco product for smokers. *Nicotine and Tobacco Research.*2008;10(3):417-21.

Other Results from Blank Study

- Heart rate (HR) was reported to increase after tablet administration, however, these increases were independent of dose
- Mean HR across doses at baseline was 68 bpm (SD=8) and rose to a max of 72 bpm (SD=7) at 10 min post dose
- Significant effect of dose and time were reported for nausea with score typically peaking at the 10 min post administration time interval
- Increased ratings were also noted for dizziness, confusion, lightheadedness, and nervousness

Tobacco Specific Nitrosamine Levels

TSNA levels are different among products, but specific correlation between biomarkers and clinical outcomes is unknown

Product	Tobacco-specific nitrosamine level (µg/g product wet weight)				
	NNN	NNK	NAT	NAB	Total
New tobacco products					
Hard snuff					
Ariva	0.019	0.037	0.12	0.008	0.19[a]
Stonewall	0.056	0.043	0.17	0.007	0.28[b]
Swedish snus					
General	0.98	0.18	0.79	0.06	2.0[c]
Spit-free tobacco packets					
Exalt					
Purchased in Sweden	2.3	0.27	0.98	0.13	3.7[d]
Purchased in the United States	2.1	0.24	0.68	0.05	3.1[b]
Revel					
Mint flavored	0.62	0.033	0.32	0.018	0.99[b]
Wintergreen flavored	0.64	0.032	0.31	0.017	1.0[b]
Tobacco-free snuff					
Smokey Mountain	nd	nd	nd	nd	nd[b]
Nicotine-reduced cigarettes					
Quest 1 (low nicotine)	0.93	0.17	0.31	0.013	1.4[d]
Quest 2 (extra-low nicotine)	0.82	0.19	0.19	0.01	1.2[d]
Quest 3 (nicotine free)	0.83	0.054	0.045	0.003	0.93[d]
Nicotine replacement therapy products					
NicoDerm CQ (patch, 4-mg nicotine)[f]	nd	0.008	nd	nd	0.008[b]
Nicorette (gum, 4-mg nicotine)[f]	0.002	nd	nd	nd	0.002[b]
Commit (lozenge, 2-mg nicotine)[f]	nd	nd	nd	nd	nd[b]

Stepanov I, et al. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res. 2006 Apr;8(2):309-13.*

2007 Study by Mendoza-Baumgart et al.

- Evaluated Ariva, Exalt, and 4 mg Commit
- CO levels among Ariva and Commit were similar as were mean urine cotinine and NNAL
- Physiological effects of Ariva were not found to be significantly different from Commit (blood pressure, heart rate, WBC and Hb levels)
- Authors caution this was a pilot study (n=49) and although Ariva use led to levels of total NNAL and cotinine similar to Commit lozenge, consumers are unaware of other potential toxicants in ST compared to approved NRT

Mendoza-Baumgart, M et al. Pilot study on lower nitrosamine smokeless tobacco products compared with medicinal nicotine. *Nicotine Tob Res*. 2007;9(12):1309-23.

Understanding Health Effects is Complex

- Disease burden of the various ST products are not necessarily the same

- Genetic factors may play an important role in determining susceptibility to cancers and other diseases from tobacco use

Important Subpopulation to Consider

- An area of health that should receive attention is the effect of DTPs on reproductive health considering women in the age range of 18-44 have a potential to become pregnant
- Traditional ST have been used predominantly by men, but DTPs may appeal to both men and women in that they are more discreet and require no spitting

Summary

- Many factors may affect consumer health such as: type & amount of tobacco constituents, number of products consumed, product dissolution characteristics, and use behavior
- More clinical research is needed as well as standardized clinical evaluation processes to understand the health effect of DTPs

Acknowledgement

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